Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. [143 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnostic Procedure

The Task Force recommends screening for vitamin D deficiency in individuals at risk for deficiency. The task force does not recommend population screening for vitamin D deficiency in individuals who are not at risk (1 | ++++).

The Task Force recommends using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter) and vitamin D insufficiency as a 25(OH) D of 21–29 ng/ml (52.5–72.5 nmol/liter). The task force recommends against using the serum 1,25-dihydroxyvitamin D [1,25(OH)2D] assay for this purpose and is in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism (1 | ++++).

Recommended Dietary Intakes of Vitamin D for Patients at Risk for Vitamin D Deficiency

The Task Force suggests that infants and children aged 0–1 yr require at least 400 IU/d (IU = 25 ng) of vitamin D and children 1 yr and older require at least 600 IU/d to maximize bone health. Whether 400 and 600 IU/d for children aged 0–1 yr and 1–18 yr, respectively, are enough to provide all the potential nonskeletal health benefits associated with vitamin D to maximize bone health and muscle function is not known at this time. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml (75 nmol/liter) may require at least 1000 IU/d of vitamin D (2 | ++++).

The Task Force suggests that adults aged 19–50 yr require at least 600 IU/d of vitamin D to maximize bone health and muscle function. It is unknown whether 600 IU/d is enough to provide all the potential nonskeletal health benefits associated with vitamin D. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1500–2000 IU/d of vitamin D (2 | ++++).

The Task Force suggests that all adults aged 50–70 and 70+ yr require at least 600 and 800 IU/d, respectively, of vitamin D to maximize bone health and muscle function. Whether 600 and 800 IU/d of vitamin D are enough to provide all of the potential nonskeletal health benefits associated with vitamin D is not known at this time. Among those age 65 and older the Task Force recommends 800 IU/d for the prevention of falls and fractures. However, to raise the blood level of 25(OH)D above 30 ng/ml may require at least 1500–2000 IU/d of supplemental vitamin D (2 | ++++).

The Task Force suggests that pregnant and lactating women require at least 600 IU/d of vitamin D and recognizes that at least 1500–2000 IU/d of vitamin D may be needed to maintain a blood level of 25(OH)D above 30 ng/ml (2 | +++O).

The Task Force suggests that obese children and adults on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for acquired immune deficiency syndrome (AIDS) be given at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement (2 | ++++).

The Task Force suggests that the maintenance tolerable upper limits (UL) of vitamin D, which is not to be exceeded without medical supervision, should be 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1 yr, at least 2500 IU/d for children aged 1–3 yr, 3000 IU/d for children aged 4–8 yr, and 4000 IU/d for everyone over 8 yr. However, higher levels of 2000 IU/d for children 0–1 yr, 4000 IU/d for children 1–18 yr, and 10,000 IU/d for children and adults 19 yr and older may be needed to correct vitamin D deficiency (2 | ++++).

Treatment and Prevention Strategies

The Task Force suggests using either vitamin D_2 or vitamin D_3 for the treatment and prevention of vitamin D deficiency (2 | ++++).

For infants and toddlers aged 0–1 yr who are vitamin D deficient, the Task Force suggests treatment with 2000 IU/d of vitamin D_2 or vitamin D_3, or with 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 400–1000 IU/d (2 | ++++).

For children aged 1–18 yr who are vitamin D deficient, the Task Force suggests treatment with 2000 IU/d of vitamin D_2 or vitamin D_3 for at least 6 wk or with 50,000 IU of vitamin D_2 once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 600–1000 IU/d (2 | ++++).

The Task Force suggests that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 wk or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d (2 | ++++).

In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, the Task Force suggests a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000–6000 IU/d (2 | ++++).

In patients with extrarenal production of $1,25(OH)_2D$, the Task Force suggests serial monitoring of 25(OH)D levels and serum calcium levels during treatment with vitamin D to prevent hypercalcemia (2 | ++++).

For patients with primary hyperparathyroidism and vitamin D deficiency, we suggest treatment with vitamin D as needed. Serum calcium levels should be monitored (2 | ++++).

Noncalcemic Benefits of Vitamin D

The Task Force recommends prescribing vitamin D supplementation for fall prevention. They do not recommend prescribing vitamin D supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (2 | ++++).

Definitions:

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of the Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Vitamin D deficiency

Guideline Category

Diagnosis

Evaluation

Prevention

Risk Assessment

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidelines to clinicians for the evaluation, treatment, and prevention of vitamin D deficiency with an emphasis on the care of patients who are at risk for deficiency

Target Population

Patients who are at risk for or who have vitamin D deficiency

Interventions and Practices Considered

Screening/Diagnosis

1. Screening individuals at risk for vitamin D deficiency
2. Serum 25-hydroxyvitamin D [25(OH)D] measurement

Treatment/Prevention

1. Vitamin D supplementation, including for fall prevention
2. Special dosage of vitamin D supplementation for:
    - Pregnant and lactating women
    - Obese children and adults
    - Patients with malabsorption syndromes
    - Children and adults on anticonvulsant medications, glucocorticoids, antifungals (such as ketoconazole), or medications for AIDs
3. Vitamin D_2 or vitamin D_3 treatment
4. Serial monitoring of 25(OH)D levels and serum calcium levels in selected patients

Note: The following were considered but not recommended: serum 1,25-dihydroxyvitamin D [1,25(OH)2D] assay (except in certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism) and vitamin D supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life.

Major Outcomes Considered

- Mortality
- Linear growth of infants
- Bone health as measured by bone mineral density (BMD) and fracture risks
- Incidence of muscle weakness and falls
- Incidence of hypercalcemia
- Functional outcomes (falls, pain, quality of life)
- Cardiovascular outcomes (death, stroke, myocardial infarction, cardiometabolic risk factors)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Task Force commissioned the conduct of two systematic reviews of the literature to inform its key recommendations.

Eligibility Criteria

Eligible studies were randomized trials that enrolled adults who received vitamin D supplementation and a concurrent comparison group that did

not receive this intervention. The researchers excluded studies in which the intervention was calcitriol or one of its analogs. The researchers were interested in studies measuring the impact of the intervention on patient-important outcomes such as death, stroke, myocardial infarction (MI), and peripheral vascular disease. Secondarily, the researchers were interested in the effect of vitamin D on cardiovascular risk factors (blood pressure, glucose, and lipids). Studies were included regardless of their language, size, or duration of patient follow-up. Ineligible references were nonrandomized studies, review articles, commentaries, and letters that did not contain original data. The researchers also excluded the studies that reported a correlation of vitamin D levels with outcomes, but in which participants did not receive an intervention to raise their vitamin D levels, making causal inferences very weak.

Study Identification

An expert reference librarian designed and conducted the electronic search strategy with input from study investigators with expertise in conducting systematic reviews. To identify eligible studies, the Task Force searched the electronic databases MEDLINE, EMBASE, Web of Science, SCOPUS, PEDRro (Physiotherapy Evidence Database); and regional medical databases (KoreanMed, Scielo, LILACs, Imbiomed, Index for Australian medical literature, Eastern Mediterranean Index, IndMed, ExtraMed) through August 2010. Search terms included vitamin D (as supplement, blood level, deficiency), vitamin D deficiency, individual metabolites of vitamin D, vitamin D_2, vitamin D_3 (explode cholecalciferols, ergocalciferols, adjusted for database-specific vocabulary), explode sunlight, hypoglycemia, hyperglycemia, blood glucose, exp diabetes mellitus; exp cardiovascular diseases, exp hypertension, ex cerebrovascular disorders/(including stroke), explode hyperlipidemia, exp lipids/bl; explode thromboembolism or explode thrombosis or cardiovascular risk (EMBASE), risk$ or mortality or incidence or prevalence or outcome, populations, specific study types such as crossover, observational studies. In addition, the Task Force reviewed the reference sections of eligible studies and available reviews and requested potentially eligible studies from content experts.

Number of Source Documents

The researchers found 51 eligible trials.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

To assist in formulating these guidelines, the reviewers conducted a systematic review of the literature to quantitatively and qualitatively summarize the available evidence regarding the possible cardiovascular harms and benefits of vitamin D.

Reviewers extracted descriptive, methodological, and outcome data from all eligible studies.

The group conducted a systematic review and meta-analysis to summarize the best available research evidence regarding the effect of vitamin D on patient-important cardiovascular events and other cardiovascular risk factors.

The group performed random-effect meta-analysis to pool relative risk (RR) and 95% confidence level (CI) across included studies. RR values under 1.00 are associated with decreased risk for a particular outcome as a result of a vitamin D-raising intervention. For continuous outcomes, the group pooled the weighted mean difference across studies. The I^2 statistic, which estimates the percentage of total variation across studies that is due to heterogeneity rather than chance, was used to assess inconsistency. I^2 values of 25% or less, 50%, and at least 75% represent low, moderate, and high inconsistency, respectively. Treatment effect-subgroup interactions were assessed by the analysis of variance (ANOVA) method and meta-regression analysis. Statistical analysis was conducted using Comprehensive Meta-Analysis, version 2 (Biostat Inc., Englewood, NJ).

The group conducted sensitivity analyses to determine whether review conclusions were affected by the choice of statistical methods (random-effects model vs. fixed-effect model) or when borderline eligible articles are included or excluded as well as the effect of excluding observational and cluster randomized studies.

See the systematic review and meta-analysis (see the "Availability of Companion Documents" field) for additional details on the data collected and the subgroup and sensitivity analyses.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Clinical Guidelines Subcommittee of The Endocrine Society appointed a Task Force to formulate evidence-based recommendations. The Task Force was composed of a Chair, six additional experts, and a methodologist.

Consensus was guided by systematic reviews of evidence and discussions during several conference calls and e-mail communications. The draft prepared by the Task Force was reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and members of The Endocrine Society, who reviewed the guidelines online. At each stage of review, the Task Force received written comments and incorporated needed changes.

Rating Scheme for the Strength of the Recommendations

Strength of the Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The draft prepared by the Task Force was reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and cosponsoring associations, and it was posted on The Endocrine Society web site for member review. At each stage of review, the Task Force received written comments and incorporated needed changes.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate management and prevention of vitamin D deficiency

Potential Harms

- Based on all of the available literature, the panel concluded that vitamin D toxicity is a rare event caused by inadvertent or intentional ingestion of excessively high amounts of vitamin D. Although it is not known what the safe upper value for 25(OH)D is for avoiding hypercalcemia, most studies in children and adults have suggested that the blood levels need to be above 150 ng/ml before there is any concern.
- Vitamin D supplementation should not be a major concern except in certain populations who may be more sensitive to it. Patients who have chronic granuloma forming disorders including sarcoidosis or tuberculosis, or chronic fungal infections, and some patients with lymphoma have activated macrophages that produce 1,25(OH)2D in an unregulated fashion. These patients exhibit an increase in the efficiency of intestinal calcium absorption and mobilization of calcium from the skeleton that can cause hypercalciuria and hypercalcemia. Thus, their 25(OH)D and calcium levels should be monitored carefully. Hypercalciuria and hypercalcemia are usually observed only in patients with granuloma-forming disorders when the 25(OH)D is above 30 ng/ml.
- There are sparse data to guide pediatric clinicians in the treatment of young children with vitamin D deficiency. One study showed that infants with vitamin D deficiency who receive doses of ergocalciferol exceeding 300,000 IU as a one-time dose were at high risk for hypercalcemia. Therefore, most pediatric providers use lower dose daily or weekly regimens. Caution also needs to be shown in children with Williams syndrome or other conditions predisposing to hypercalcemia

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. [143 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Jul

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

The Endocrine Society

The Task Force received no corporate funding or remuneration.

Guideline Committee

Evaluation, Treatment, and Prevention Vitamin D Deficiency Task Force

Composition of Group That Authored the Guideline

Task Force Members: Michael F. Holick (*Chair*); Neil C. Binkley; Heike A. Bischoff-Ferrari; Catherine M. Gordon; David A. Hanley; Robert P. Heaney; M. Hassan Murad; Connie M. Weaver

Financial Disclosures/Conflicts of Interest

Michael F. Holick, Ph.D., M.D. (chair)—Financial or Business/Organizational Interests: Merck, Novartis, Nichols-Quest Diagnostics, Bayer, Aventis, Warner Chilcott, Amgen, UV Foundation, Mushroom Council and Dairy Management, Inc.; Significant Financial Interest or Leadership Position: none declared.

Neil C. Binkley, M.D.—Financial or Business/Organizational Interests: American Society for Bone and Mineral Research, International Society for Clinical Densitometry; Significant Financial Interest or Leadership Position: none declared.

Heike A. Bischoff-Ferrari, M.D., Dr.P.H.—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared.

Catherine M. Gordon, M.D., M.Sc.—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: Co-Director, Clinical Investigator Training Program (Harvard/MIT with Pfizer/Merck).

David A. Hanley, M.D., FRCPC—Financial or Business/Organizational Interests: Canadian Society of Endocrinology and Metabolism, Osteoporosis Canada, International Society for Clinical Densitometry; Advisory Boards: Amgen Canada, Merck Frosst Canada, Eli Lilly Canada, Novartis Canada, Warner Chilcott Canada; Significant Financial Interest or Leadership Position: Past President of Canadian Society of Endocrinology and Metabolism.

Robert P. Heaney, M.D.—Financial or Business/Organizational Interests: Merck, Procter & Gamble; Significant Financial Interest or Leadership Position: none declared.

M. Hassan Murad, M.D.*—Financial or Business/Organizational Interests: KER Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared.

Connie M. Weaver, Ph.D.—Financial or Business/Organizational Interests: Pharmavite; Significant Financial Interest or Leadership Position: National Osteoporosis Foundation.

*Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

Guideline Endorser(s)

Canadian Society of Endocrinology and Metabolism - Medical Specialty Society

National Osteoporosis Foundation - Disease Specific Society

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from The Endocrine Society Web site .

Print copies: Available from The Endocrine Society, Phone: (301) 941.0210; Email: Societyservices@endo-society.org.

Availability of Companion Documents

The following are available:

- Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Hazem A, Erwin PJ, Hensrud DD, Murad MH, Montori VM. Clinical review: vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011 96:1931-1942. Electronic copies: Available to subscribers from the Journal of Clinical Endocrinology & Metabolism Web site .
- Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, Almandoz JP, Mullan RJ, Lane MA, Liu H, Erwin PJ, Hensrud DD, Montori VM. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Oct;96(10):2997-3006. Epub 2011 Jul 27. Available to subscribers from the Journal of Clinical Endocrinology & Metabolism Web site .

Patient Resources

The following is available:

- Patient guide to vitamin D deficiency. The Hormone Foundation. 2011 Jul. 2 p. Electronic copies: Available in Portable Document Format (PDF) from The Hormone Foundation Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on January 10, 2012. The information was verified by the guideline developer on February 3, 2012.

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